

#### REMARKS

Reconsideration of the present application is respectfully requested in view of the above amendments and the following remarks. Claims 27-56 are pending and currently under examination in the application. Without acquiescence or prejudice to pursuing the encompassed subject matter in a related application, claims 28, 34, 40, and 46 are canceled, and claims 27, 29-33, 35-39, 41-45, 47-50, and 52 are amended to more particularly point out and distinctly claim certain embodiments of Applicant's invention. No new matter has been added by these amendments. Support for the amendments can be found in the claims and in the specification as originally filed, for example, in original claim 1.

#### DECLARATION

The Examiner states that the Declaration filed with Applicant's response of August 19, 2008 does not identify the rule under which it was filed. The Examiner kindly invites Applicant to correct the Declaration in this response.

Applicant thanks the Examiner for noting this inadvertent error, and states for the record that the Declaration of Dr. Tracey Brown of record in this case was filed under 37 C.F.R. § 1.132.

#### REJECTIONS UNDER 35 U.S.C. § 102, ALTERNATIVELY § 103

Claims 27, 33, 39, and 45 stand rejected under 35 U.S.C. § 102(e) for alleged lack of novelty, or, in the alternative, under 35 U.S.C. § 103(a) for alleged obviousness over Falk *et al.* (U.S. Patent No. 5,985,850). Essentially, the Examiner asserts that Falk *et al.* teach the use of hyaluronan within the claimed molecular weight range of 400,000 and 900,000 Da in combination with an anti-neoplastic agent, and further asserts that the method of Falk *et al.* would inherently enhance the efficacy of the agent for a cancer cell.

Applicant traverses this rejection and submits that the instant claims satisfy the requirements of novelty and non-obviousness over Falk *et al.* Nonetheless, without acquiescence or prejudice, embodiments of the instant claims as amended herewith relate, in pertinent part, to

methods of administering systemically to a subject in need thereof an effective amount of hyaluronan and said chemotherapeutic agent, wherein the hyaluronan has a molecular weight between 750,000 and 900,000 Da, and to related pharmaceutical compositions.

Falk *et al.* fail to disclose each feature of the instant claims, inherently or otherwise, and further fail to render these claims obvious. In particular, as previously made of record, Falk *et al.* fail to disclose the administration of hyaluronan and a chemotherapeutic agent, wherein the hyaluronan has a molecular weight between 750,000 and 900,000 Da, as recited in the instant claims. To the contrary, Falk *et al.*, at best, disclose hyaluronan of less than 750,000 Da, with preferred embodiments being much lower in molecular weight, *i.e.*, 150,000 to 225,000 Da. Indeed, it is kindly submitted that the Examiner recognizes this deficiency of Falk *et al.* by not rejecting previous claims 28, 34, 40, and 46 for either obviousness or lack of novelty over this reference. Accordingly, the subject matter of these claims is incorporated by present amendment into independent claims 27, 33, 39, and 45 and thus the present claims are allowable over Falk *et al.* Given the deficiencies in Falk *et al.*, this reference fails to either anticipate or render obvious the instant claims.

Therefore, Applicant submits that the instant claims satisfy the requirements of novelty and non-obviousness over Falk *et al.*, and respectfully request withdrawal of this rejection under 35 U.S.C. § 102(e), alternatively § 103(a).

#### **REJECTION UNDER 35 U.S.C. § 102**

Claims 27, 33, 39, and 45 stand rejected under 35 U.S.C. § 102(b) for alleged lack of novelty over della Valle *et al.* (U.S. Patent No. 5,422,053). Mainly, the Examiner asserts that della Valle *et al.* disclose the use of compositions comprising chemotherapeutic agents in combination with HA having a molecular weight between 300,000 and 730,000 Da.

Applicant traverses this rejection and submits that the instant claims are novel over della Valle *et al.* As noted above, the instant claims relate, in pertinent part, to methods of administering systemically to a subject in need thereof an effective amount of hyaluronan and said chemotherapeutic agent, wherein the hyaluronan has a molecular weight between 750,000 and 900,000 Da, and to related pharmaceutical compositions.

della Valle *et al.* fail to disclose each feature of the instant claims. For instance, della Valle *et al.* fail to disclose the use of hyaluronan and a chemotherapeutic agent, wherein the hyaluronan has a molecular weight between 750,000 and 900,000 Da, as recited in the instant claims. Rather, as relied upon by the Examiner, della Valle *et al.* merely disclose hyaluronan having a molecular weight of 730,000 Da or less, which does not read on the instant claims. As with Falk *et al.*, the Examiner recognizes this deficiency of della Valle *et al.* by not rejecting previous claims 28, 34, 40, and 46 for lack of novelty over this reference, the subject matter of which claims is incorporated by present amendment into independent claims 27, 33, 39, and 45. Accordingly, it is respectfully submitted that the present claims are allowable over della Valle *et al.*

In addition to the above, della Valle *et al.* fail to disclose the active, recited step of administering the claimed compositions systemically to a subject in need thereof. To the contrary, this reference is expressly limited to teaching intra-ocular, intra-articular, intradermal, and topical administration. Given the noted deficiencies in della Valle *et al.*, this reference fails to anticipate the instant claims.

Accordingly, Applicant submits that the instant claims satisfy the requirements of novelty over della Valle *et al.*, and respectfully request withdrawal of this rejection under 35 U.S.C. § 102(b).

#### **REJECTION UNDER 35 U.S.C § 103**

Claims 27-56 stand rejected under 35 U.S.C. § 103(a) for alleged obviousness over della Valle *et al.* The Examiner agrees that della Valle *et al.* do not disclose hyaluronan having a molecular weight of 750,000 Da or above in a composition with a chemotherapeutic agent, as presently claimed, but asserts that provided with the suggestion in this reference to utilize higher molecular weight hyaluronan, a person of ordinary skill in the art would have had a reasonable expectation of success in creating such a composition to provide a carrier vehicle having the desired viscosity, and, thus, to provide the desired therapeutic benefits of improved drug efficacy. With regard to Applicant's evidence on the non-obviousness of the instant claims, the Examiner further asserts that the Declaration of Tracey Brown merely represents "opinion"

evidence, as this Declaration allegedly fails to account for the effects of concentration on viscosity, especially as those effects relate to the expectations of utilizing higher molecular weight hyaluronan in the fashion claimed by Applicant.

Applicant traverses this rejection and submits that the instant claims satisfy the requirements of non-obviousness over della Valle *et al.* Applicant submits that the Examiner has not established a *prima facie* case of obviousness. See *In re Mayne*, 104 F.3d 1339 (Fed. Cir. 1997) (The USPTO has the burden of showing a *prima facie* case of obviousness).

At a minimum, the Examiner must demonstrate that the cited reference teaches or suggests all the claim features, and even assuming, *arguendo*, that the cited reference teaches each claim feature, the Examiner must provide an explicit, apparent reason to combine these features in the fashion claimed by the Applicant with a reasonable expectation of success. See *KSR v. Teleflex, Inc.*, No. 04-1350 at 4, 14 (U.S. Apr. 30, 2007) ("A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art"). Here, the Examiner has neither established that della Valle *et al.* teach or suggest each claim feature, nor has the Examiner established that this reference provides any reason to administer systemically to a subject higher molecular weight hyaluronan, as presently claimed, with a reasonable expectation of success.

della Valle *et al.* fail to teach or suggest each feature of the instant claims. In particular, regardless of the Examiner's assertion that della Valle *et al.* may *suggest* the use of hyaluronan having a molecular weight higher than 730,000 Da, this reference does not teach or suggest administering systemically to a subject an effective amount of hyaluronan and a chemotherapeutic agent, wherein the hyaluronan has a molecular weight between 750,000 and 900,000 Da. Rather, as noted above, della Valle *et al.* are expressly limited to teaching intra-ocular, intra-articular, intradermal, and topical administration, none of which relates to the suitability of a given composition for systemic administration, as presently claimed and discussed herein. By failing to show that della Valle *et al.* teach or suggest each feature of the instant claims, Applicant submits that the Examiner has not established the requisite elements of a *prima facie* case of obviousness over the presently claimed subject matter.

Moreover, it is respectfully submitted that the Examiner has not established by the requisite technical reasoning that a person skilled in the art would have practiced the presently claimed subject matter with a reasonable expectation of success. *see KSR* at 14, citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) (“[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.”). For instance, the Examiner has not shown that such a person would have reasonably expected a composition of hyaluronan having a molecular weight of 750,000-900,000 Da to be suitable for systemic administration, let alone would that person have expected it to provide a carrier having a viscosity suitable for enhancing the efficacy of a chemotherapeutic agent to a cancer cell. Instead, the Examiner relies on the assertion that a person skilled in the art “would reasonably expect that hyaluronic acid having molecular weights greater than 730,000 *would be applicable to della Valle*” (*see* the Action, page 9) (emphasis added). However, Applicant submits that the asserted applicability of such subject matter to della Valle *et al.* does not establish its applicability to the instant methods, because, as noted above, della Valle *et al.* are expressly limited to intra-ocular, intra-articular, intradermal, and topical administration, and teach or suggest nothing about systemic administration, as presently claimed. In this regard, it is respectfully submitted that the limited teachings of della Valle *et al.*, as relied upon by the Examiner, fail to address the concerns and expectations with regard to systemic administration, and, thus, fail to support of the Examiner’s burden of proof in establishing a *prima facie* case of obviousness.

These deficiencies in the Examiner’s technical reasoning are especially acute in view of Applicant’s evidence of record (*see* the Declaration of Dr. Tracey Brown), which not only teaches away from administering systemically to a subject a composition comprising hyaluronan having a modal molecular weight between 750,000 and 900,000 Da, as presently claimed, but evidences the unexpected results obtained therefrom. Even though this Declaration does not specifically mention della Valle *et al.*, as asserted by the Examiner (*see* the Action, page 10), the empirical evidence contained therein speaks clearly to the non-obviousness of the instant claims. In particular, as previously made of record, this Declaration teaches that compositions of

hyaluronan having increased molecular weight (*e.g.*, 750,000 Da or above) are highly viscous, such that in the absence of Applicant's experimental evidence their systemic or intravenous administration would have been expected to lead to either hyper-viscosity syndrome, the formation of occlusions to blood vessels, and/or the formation of emboli or thrombosis (*see, e.g.*, Item 8 of the Declaration of T. Brown), none of which represent a desired therapeutic outcome. Consistent with this understanding, della Valle *et al.* similarly teach that the higher weight hyaluronan compositions described therein have high viscosity, making them suitable only for limited therapeutic purposes, such as topical, intra-ocular, and intra-articular administration (*see, e.g.*, column 3, lines 62-64; and column 4, lines 13-23). The evidence of record, therefore, not only contradicts the Examiner's asserted reasonable expectation of success in arriving at the presently claimed subject matter, but teaches away from the same, thereby supporting a conclusion of non-obviousness under § 103(a).

Further, Applicant respectfully disagrees with the Examiner's analysis of the Declaration of Dr. Tracey Brown. Specifically, it is kindly submitted that the Examiner overlooks certain of the details contained in this Declaration, and thereby errs in asserting that the Declaration fails to take into account the effect of hyaluronan concentration on viscosity (*see* the Action, pages 10-11, carryover sentence). A closer look at the Declaration reveals empirical evidence that relates the viscosity of hyaluronan to both its molecular weight and its concentration (**2.5 mg/ml**) (*see* the Table in Item 8); especially for the concentration of hyaluronan used in successful phase I clinical trials (**2mg/ml to 4mg/ml**) (*see* Item 8, last paragraph). Thus, and contrary to the Examiner's assertion (*see* the Action, page 10, last sentence), the Declaration of Dr. Brown represents more than just "opinion" evidence, but rather provides empirical evidence of teaching away and unexpected results, thereby showing that a person skilled in the art would have had no reasonable expectation of success in utilizing higher molecular weight hyaluronan-based compositions for systemic administration in cancer therapy.

Given the deficiencies of della Valle *et al.*, especially in view of Applicant's evidence on teaching away and unexpected results, Applicant submits that the instant claims satisfy the requirements of non-obviousness over this reference. Applicant, thus, respectfully requests withdrawal of this rejection under 35 U.S.C. § 103(a).

Applicant believes that all of the claims in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,  
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